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Original Contribution

Maternal Alcohol Consumption, Alcohol Metabolism Genes, and the Risk of Oral Clefts: A Population-based Case-Control Study in Norway, 1996–2001

Abee L. Boyles*, Lisa A. DeRoo, Rolv T. Lie, Jack A. Taylor, Astanand Jugessur, Jeffrey C. Murray, and Allen J. Wilcox

* Correspondence to Dr. Abee L. Boyles, Epidemiology Branch, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, P.O. Box 12233, MD A3 05, Durham, NC 27709 (e-mail: boylesa@niehs.nih.gov).

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Heavy maternal alcohol consumption during early pregnancy increases the risk of oral clefts, but little is known about how genetic variation in alcohol metabolism affects this association. Variants in the alcohol dehydrogenase 1C (*ADH1C*) gene may modify the association between alcohol and clefts. In a population-based case-control study carried out in Norway (1996–2001), the authors examined the association between maternal alcohol consumption and risk of oral clefts according to mother and infant *ADH1C* haplotypes encoding fast or slow alcohol-metabolizing phenotypes. Subjects were 483 infants with oral cleft malformations and 503 control infants and their mothers, randomly selected from all other livebirths taking place during the same period. Mothers who consumed 5 or more alcoholic drinks per sitting during the first trimester of pregnancy had an elevated risk of oral cleft in their offspring (odds ratio (OR) = 2.6, 95% confidence interval (CI): 1.4, 4.7). This increased risk was evident only in mothers or children who carried the *ADH1C* haplotype associated with reduced alcohol metabolism (OR= 3.0, 95% CI: 1.4, 6.8). There was no evidence of alcohol-related risk when both mother and infant carried only the rapid-metabolism *ADH1C* variant (OR = 0.9, 95% CI: 0.2, 4.1). The teratogenic effect of alcohol may depend on the genetic capacity of the mother and fetus to metabolize alcohol.

alcohol drinking; alcoholic beverages; cleft lip; cleft palate; genetic research; maternal exposure; pregnancy

Abbreviations: ADH, alcohol dehydrogenase; ADH1B, alcohol dehydrogenase 1 B; ADH1C, alcohol dehydrogenase 1 C; ALDH1A, aldehyde dehydrogenase 1 A; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

Alcohol is an established human teratogen (1). We previously found that women who consumed 5 or more alcoholic drinks per sitting during the first trimester of pregnancy had a markedly increased risk of oral clefts in their offspring (2). Such teratogenic effects of alcohol might be sensitive to genetic differences in alcohol metabolism. If the mother and fetus have reduced metabolism rates, a given level of alcohol consumption could expose the fetus to higher peak levels of alcohol for longer periods of time.

Alcohol is metabolized in 2 steps: alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde, which is then oxidized to acetate by aldehyde dehydrogenase. A major variant of the alcohol dehydrogenase 1 C (*ADH1C*) gene with 2 amino acid differences produces functional changes in a person's capacity to oxidize alcohol (3). This gene variant has been implicated in the risk of alcohol-associated cancers of the colon and rectum, esophagus, and head and neck (4–6).

With regard to clefting, our recent search of more than 300 candidate genes for oral clefts identified the *ADH1C* gene as a risk factor for cleft lip and palate in Norwegians (independent of alcohol consumption), with replication of this association in a separate population (7). We explored the possibility that *ADH1C* variants modify the teratogenic effects of maternal alcohol drinking. If such interactions were found, they could add to the evidence for a causal role of alcohol in facial clefts (8).

MATERIALS AND METHODS

Study design

We carried out a population-based case-control study of babies born in Norway between 1996 and 2001 with oral clefts. Details have been given elsewhere (9). All Norwegian infants with oral clefts are referred to one of 2 surgical centers for free surgical treatment. Through these centers, we invited all families of newly diagnosed infants to participate in a research study. Of approximately 300,000 livebirths taking place during this period, 676 infants with oral clefts were referred for surgery. Families were not eligible if the infant died or the mother did not speak Norwegian ($n = 24$); this left 652 eligible families. Of these families, 88% agreed to participate ($n = 573$), and all provided some DNA. Controls were randomly selected from all other livebirths occurring during the same time period using the same exclusion criteria; 76% of the families that were invited and were eligible agreed to participate ($n = 763$), and 762 provided DNA for the mother, father, or infant. All parents provided informed consent.

Data collection

Biologic samples. Case parents donated blood samples for themselves and their infants that were collected at the time of the infant's corrective surgery. Control families provided cheek-swab samples collected by mail. Blood samples collected at birth for phenylketonuria testing were also available for all infants. None of the samples required whole-genome DNA amplification.

Questionnaire data. Mothers completed a self-administered, mailed questionnaire on demographic characteristics, medical history, family history of oral clefts, pregnancy characteristics, and maternal exposures during pregnancy. Median time from the baby's delivery to the mother's completion of the questionnaire was 14 weeks for cases and 15 weeks for controls.

Mothers were asked about their alcohol consumption during the first 3 months of pregnancy, which is the relevant period for early facial development. Closure of the lip occurs in weeks 5–6 postconception, followed by closure of the palatal shelves in weeks 7–10 (10). Mothers were asked to recall the average number of days per week or month on which they drank alcoholic beverages and the average number of drinks consumed on each occasion. Evidence from animal and human studies suggests that the dose of alcohol rather than the frequency or total amount consumed is the most relevant exposure for fetal outcomes (11). Consistent with this, the maternal alcohol variable most strongly associated with oral clefts in our data was the average number of drinks consumed per sitting (2). We used a categorical variable summarizing average number of drinks per sitting (0, 1–4, or ≥ 5), with the abstainers serving as the referent group.

Sample processing and candidate gene assays

DNA was extracted from blood for case families and from cheek swabs for control families. Blood samples from phenylketonuria testing were used if DNA was not available for the case or control infants. Genetic assays were part of a larger project exploring candidate genes for oral clefts. A custom panel of 1,536 single nucleotide polymorphisms (SNPs) for 357 genes plausibly related to oral cleft risk was selected, and genotyping was conducted by the Center for Inherited Disease Research (http://www.cidr.jhmi.edu) at the Johns Hopkins University (Baltimore, Maryland). Gene and SNP selection, data cleaning, and quality-control measures have been described elsewhere (7). For the present analysis, fathers' genotypes were used only to identify Mendelian inconsistencies.

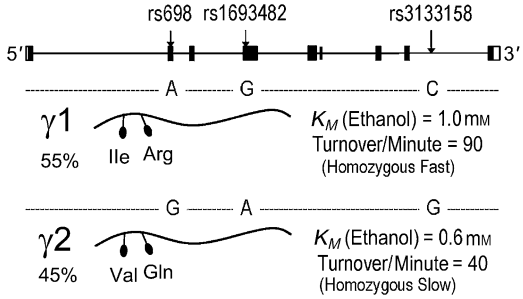

Figure 1. Location of 3 single nucleotide polymorphisms (rs698, rs1693482, and rs3133158) within the alcohol dehydrogenase 1 C (*ADH1C*) gene. Boxes indicate exons, and lines indicate introns. Using the 3 single nucleotide polymorphisms, the authors identified 2 haplotypes (dotted lines with letters) encoding proteins (curved lines) with different Michaelis-Menten enzymatic kinetics (3). The frequencies of the γ1 and γ2 variants in Caucasian populations are indicated. K_M refers to the concentration of ethanol (mM) at which the enzyme works at 50% capacity. Turnover is the number of ethanol molecules converted to acetaldehyde in 1 minute at saturating alcohol concentrations.

We focused on genetic variations in the ADH enzymes that oxidize ethanol to acetaldehyde. SNPs in the aldehyde dehydrogenase 1 A (*ALDH1A*) gene from the candidate gene study were not associated with oral clefts, and we did not examine them here. Seven *ADH* genes encode proteins that can function as heterodimers with varying affinities for ethanol (3). Some polymorphisms in these genes alter the rate of ethanol oxidation. *ADH* genes are expressed in the human placenta during the first trimester of pregnancy (12); thus, fetal as well as maternal genes may play a role in ethanol metabolism. We assessed the influence of both the mother's and the embryo's genotypes on the teratogenic effects of alcohol.

We focused on the *ADH1C* gene, which has functional SNPs that are common in Europeans and was associated with oral clefts in both the Norwegian and Danish populations. We also had data on other variants of *ADH* genes, including alcohol dehydrogenase 1 B (*ADH1B*), which has been reported to modify the effect of maternal alcohol consumption on fetal alcohol syndrome (another condition stemming from maternal alcohol consumption during pregnancy) (13–15). However, this *ADH1B* variant is uncommon in Europeans, which a priori made it a less promising candidate for study in Norwegians. None of the other *ADH* genes were associated with risk of oral clefts.

Our custom genotyping panel included 3 *ADH1C* SNPs (Figure 1) in very high linkage disequilibrium (all pairwise

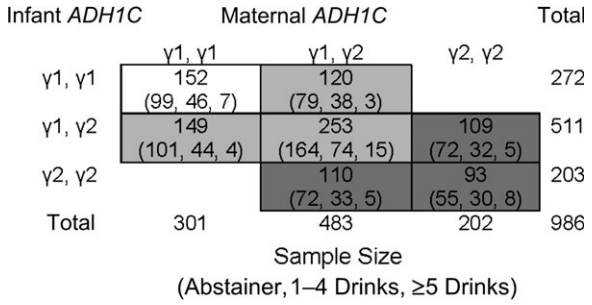

Figure 2. Distribution of maternal-infant pairs according to possession of variants in the alcohol dehydrogenase 1 C (*ADH1C*) gene and maternal alcohol drinking status, Norway, 1996–2001. Shading denotes the 3 combined maternal and infant *ADH1C* alcohol-metabolizing activity groups: white = high activity, light gray = intermediate activity, and dark gray = low activity. The term "reduced activity" in the text and other figures refers to the intermediate and low-activity groups combined.

$D' \geq 0.99$ and $r^2 \geq 0.59$, calculated in the control population with Haploview, version 4.0 (16)). Two of the SNPs are nonsynonymous: rs1693482 converts an arginine to a glutamine at position 272, and rs698 converts an isoleucine to a valine at position 350. We identified 2 haplotypes previously described as *ADH1C**1 encoding γ1 (Arg272, Ile350) and *ADH1C**2 encoding γ2 (Gln272, Val350) (Figure 1) (3). A third SNP, rs3133158, is located in the eighth intron 6.6 kilobases from rs1693482 and was used to identify the haplotype for subjects missing other genotypes. The major C allele of rs3133158 was associated with the *ADH1C**1 haplotype, while the minor G allele was found with the *ADH1C**2 haplotype. Haplotypes were inferred for 29 subjects missing one of the 3 SNPs and for 1 subject missing 2.

The 2 ADH1C protein variants have well-characterized metabolic properties. γ1 is the faster metabolizing enzyme, while γ2 has a slower metabolizing phenotype quantified by Michaelis-Menten enzyme kinetics ($K_M = 0.6$ as compared with 1.0 and a 56% reduction in ethanol turnover rate, when comparing homozygotes of each haplotype) (3). Heterozygotes have ethanol metabolism rates that are intermediate between those of the homozygotes (17). We studied the 3 haplotype combinations in mothers and offspring separately and then examined maternal-infant genotypes together. We dichotomized maternal-infant genotypes into "high activity" ($n = 152$; both mother and infant had 2 copies of the fast variant) and "reduced activity" ($n = 834$; either the mother or the infant had the slower variant). The latter group was further subdivided into "intermediate activity" ($n = 522$; either the mother or the infant had 1 copy of the slow variant, but neither had 2 copies) and "low activity" ($n = 312$; either or both had 2 copies of the slow variant) (Figure 2).

Statistical analysis

We analyzed data from 995 infant-mother pairs (488 cases and 507 controls) for whom an *ADH1C* genotype was available for both subjects (75% of all participants). Eleven case families and 170 control families had not been included in the previous candidate gene study, and therefore genotypes were unavailable; in addition, 18 families were removed because of Mendelian inconsistencies (7). Other families had no available *ADH1C* genotypes for the mother ($n = 41$), the child ($n = 111$), or both ($n = 7$). Of the 995 genotyped pairs, 5 mothers of cases and 4 mothers of controls were missing information on alcohol consumption, yielding 483 case-mother pairs and 503 control-mother pairs for analysis. Genotypes were tested for Hardy-Weinberg equilibrium as a quality-control measure in the candidate-gene study, and again in this subset using a 2-df χ^2 goodness-of-fit test (18). Clinicians from the referring surgical centers identified the type of oral cleft; 313 infants had cleft lip with or without cleft palate, and 170 had cleft palate only (19). Cases and controls included infants with noncleft malformations, including syndromes. Limiting the analysis to infants without other malformations produced little change in the results (data not shown).

Genes related to alcohol metabolism have been associated with behavioral patterns of alcohol drinking (20). We assessed whether women's consumption of alcohol was related to their *ADH1C* haplotypes using a Pearson χ^2 test with 4 df.

We used logistic regression to calculate odds ratios and 95% confidence intervals for the associations between oral clefts and maternal alcohol consumption, stratified by maternal and infant *ADH1C* genotypes. The association between oral clefts and maternal alcohol consumption was similar for cleft lip with or without cleft palate and cleft palate only (2), so the 2 case groups were combined for most analyses. Multivariable model results were adjusted for potential confounders: infant's birth year and maternal smoking, age, education, marital status, and folate supplementation. To test for interaction of maternal alcohol consumption and *ADH1C* genotype on a multiplicative scale, we created a product term for the interaction between the 2 variables and used likelihood ratio tests to compare models with and without the interaction term.

Variants of *ADH1B* also have strong biologic activity. The widely studied A allele of rs1229984 leads to an especially fast rate of alcohol metabolism (88-fold increase) (3), but these variants were too uncommon in our population for separate analysis. We repeated our analyses after removing subjects with this polymorphism to see whether the polymorphism could be contributing to our results. We expected that removing mothers and infants with this fast-metabolizing *ADH1B* variant would strengthen any effects of slower metabolism due to the *ADH1C* polymorphism.

RESULTS

Table 1 provides a description of the study participants. Three percent of control mothers and 7% of case mothers reported consuming an average of 5 or more alcoholic drinks per sitting during the first trimester of pregnancy. Study subjects were distributed across 7 possible mother-infant *ADH1C* genotype combinations (Figure 2).

Previous reports have suggested that *ADH1C* variants may influence alcohol consumption (21, 22). In our data,

Table 1. Characteristics of Infants With Oral Clefts and Control Infants and Their Mothers, Norway, 1996–2001

	Cases (n = 483)		Controls (n = 503)	
	No.	%	No.	%
Maternal characteristics				
Age, years				
<25	87	18	77	15
25–29	185	38	204	41
30–34	150	31	148	29
≥35	61	13	74	15
Marital status				
Married	233	48	269	54
Living as married	230	48	219	44
Single[a]	19	4	14	3
Missing data	1		1	
Educational level				
Less than high school	79	16	47	9
High school	122	25	134	27
Technical college	91	19	96	19
2–4 years of college (i.e., Bachelor's degree)	162	34	194	39
University (i.e., Master's degree or more)	29	6	32	6
Parity				
1	205	42	194	39
2	167	35	191	38
3	85	18	84	17
≥4	26	5	34	7
Cigarette smoking[b]				
No smoke exposure	208	43	270	54
Passive exposure only	75	16	75	15
Active smoker, cigarettes/day				
1–5	108	22	93	19
6–10	69	14	49	10
≥11	23	5	16	3
Folic acid supplementation, μg/day[c]				
0	306	63	296	59
1–399	108	22	118	23
≥400	69	14	89	18
Alcohol consumption, drinks/sitting[b]				
Abstainer	294	61	348	69
1–4	157	33	140	28
≥5	32	7	15	3
Maternal *ADH1C* haplotype				
γ1,γ1	144	30	157	31
γ1,γ2	240	50	243	48
γ2,γ2	99	20	103	20
HWE χ^2 (P value)[d]	0.003 (0.998)		0.25 (0.882)	
Infant characteristics				
Noncleft birth defect	118	24	25	5
Infant *ADH1C* haplotype				
γ1,γ1	132	27	140	28
γ1,γ2	242	50	269	53
γ2,γ2	109	23	94	19
HWE χ^2 (P value)[d]	0.009 (0.995)		3.1 (0.212)	

Abbreviations: ADH1C, alcohol dehydrogenase 1 C; HWE, Hardy-Weinberg equilibrium.

[a] Includes never married, divorced, and separated.

[b] During the first 3 months of pregnancy.

[c] During the month prior to pregnancy and the first 2 months of pregnancy.

[d] HWE goodness-of-fit test with 2 df.

Table continues

there were only small differences in binge drinking among the groups (4% in γ1,γ1 high activity; 5% in γ1,γ2 intermediate activity; and 6% in γ2,γ2 low activity); these differences were consistent with chance ($P = 0.63$).

As we reported previously (2), women who drank alcohol at binge levels had over twice the risk of having an infant with an oral cleft compared with abstainers (in this subset, odds ratio (OR) = 2.6, 95% confidence interval (CI): 1.4, 4.7) (Figure 3). Independently of alcohol consumption, the association between *ADH1C* and clefts was small among mother-infant pairs who had any reduced-activity *ADH1C* variants as compared with those who had only highly active variants (OR = 1.2, 95% CI: 0.9, 1.7).

When examining maternal and infant genotypes separately, there were no clear patterns of increased risk of oral clefts from maternal binge drinking among subjects with *ADH1C* variants with reduced activity (see Web Table 1, which is posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/)). However, when we examined maternal and infant genotypes together, a more striking pattern emerged. Risk associated with alcohol drinking was evident only when the mother or infant carried the *ADH1C* haplotype with reduced activity and the mother consumed alcohol (for 1–4 drinks/sitting, OR = 1.4 (95% CI: 0.9, 2.2), and for ≥5 drinks/sitting, OR = 3.0 (95% CI: 1.4, 6.8), with high-activity abstainers designated the reference group) (Figure 3). There was no evidence of increased risk of clefts with maternal drinking when the mother and infant both had high-activity variants (0.9 for both moderate and binge-level drinking as compared with abstainers). The results were very similar for cleft lip with or without cleft palate and cleft palate only (see Web Figure). When we subdivided mothers and infants further, the risk of oral clefts with binge drinking versus abstaining was greatest among the intermediate-activity mothers and infants (unadjusted OR = 5.6, 95% CI: 1.8, 16.7) (Table 2). The risk with binge

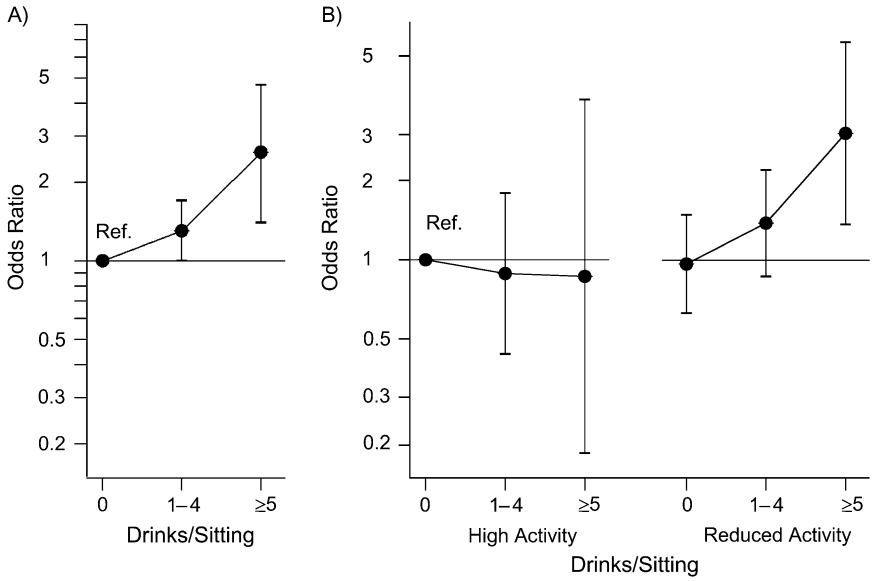

Figure 3. Odds ratios for oral clefts in offspring according to maternal alcohol consumption during the first trimester of pregnancy for A) all alcohol dehydrogenase 1 C (*ADH1C*) genotypes together and B) *ADH1C* genotypes stratified by combined mother and infant *ADH1C* alcohol-metabolizing activity (high and reduced), Norway, 1996–2001. "Reduced activity" includes the intermediate and low-activity groups combined. The referent group (Ref.) in panel B is high-activity abstainers. Bars, 95% confidence interval.

drinking increased less among the low-activity mothers and infants (among whom at least 1 had 2 copies of the slow-metabolizing haplotype) (OR = 1.8, 95% CI: 0.7, 4.7). Adjusting for potential confounders did not substantially affect most risk estimates; the odds ratio for the intermediate-activity group was mildly attenuated (adjusted OR = 4.5, 95% CI: 1.4, 14.3). A lower threshold for binge drinking (≥4 drinks/sitting) also did not appreciably change the risk estimates (see Web Table 2).

As expected, there were too few subjects with the *ADH1B* variant for fast alcohol metabolism for separate analysis: 31 mothers (3%) and 39 offspring (4%) carried

Table 2. Association Between Maternal Alcohol Consumption During the First Trimester of Pregnancy and Risk of Oral Clefts in Offspring, According to Combined Maternal and Infant Alcohol Dehydrogenase 1C Alcohol-Metabolizing Activity, Norway, 1996–2001

Analysis and Maternal Alcohol Drinking Category	Maternal and Infant *ADH1C* Activity Group						*P*-Interaction[a]
	High Activity[b]		Reduced Activity				
			Intermediate Activity[c]		Low Activity[d]		
	OR	95% CI	OR	95% CI	OR	95% CI	
Unadjusted analysis							
Abstainer	1.0	Referent	1.0	Referent	1.0	Referent	0.20
1–4 drinks/sitting	0.9	0.4, 1.8	1.4	0.9, 2.0	1.5	0.9, 2.5	
≥5 drinks/sitting	0.9	0.2, 4.1	5.6	1.8, 16.7	1.8	0.7, 4.7	
Adjusted analysis[e]							
Abstainer	1.0	Referent	1.0	Referent	1.0	Referent	0.15
1–4 drinks/sitting	0.8	0.3, 2.0	1.4	0.9, 2.1	1.4	0.8, 2.4	
≥5 drinks/sitting	0.5	0.1, 3.8	4.5	1.4, 14.3	1.5	0.5, 4.5	

Abbreviations: ADH1C, alcohol dehydrogenase 1 C; CI, confidence interval; OR, odds ratio.
[a] Multiplicative scale.
[b] Both mother and infant were homozygous fast.
[c] Either mother or infant was heterozygous, but neither was homozygous slow.
[d] Either mother or infant or both were homozygous slow.
[e] Adjusted for infant's birth year and for maternal smoking, age, education, marital status, parity, and folic acid supplementation.

the allele (53 mother-infant pairs). When we removed these subjects from the analysis, the risk estimate was slightly increased for maternal binge-level drinking among pregnancies in the intermediate-activity group (the odds ratio increased from 5.6 to 6.8), with smaller changes in other risk estimates.

DISCUSSION

Our data suggest that variants in alcohol-metabolizing genes can modify the teratogenic effect of maternal alcohol consumption. The association of heavy alcohol drinking with the risk of oral clefts was present only if either the mother or the baby carried the *ADH1C* variant that reduced ethanol-to-acetaldehyde oxidation. There was no evidence of risk from alcohol drinking if the mother and infant both had only high-activity variants, and there was no evidence of risk from *ADH1C* genotype if the mother abstained.

This association is credible on several counts. First, the study was large and population-based, with detailed information on exposures that was collected soon after delivery and DNA samples from a high proportion of infants and their parents. Second, the teratogenicity of alcohol has been demonstrated in animal models (23). A possible mechanism for alcohol-induced embryonic malformations is ethanol inhibition of retinoic acid synthesis during embryogenesis (24, 25). When consumed at high levels, ethanol competitively inhibits the production of retinoic acid (a metabolite of vitamin A), which is necessary for normal cranial neural crest development. Furthermore, alcohol is established as a teratogen in humans, most clearly in the etiology of fetal alcohol syndrome (1). Third, genetic variations in alcohol metabolism plausibly modify the effective dose of a given amount of maternal drinking, as suggested by the absence of any effect of binge drinking in the high-activity group in our study.

Both the gene and the exposure have been associated with oral clefts. In our data, heavy alcohol consumption was associated with oral clefts without regard to genotype. This has been seen in some other epidemiologic studies (26–28), though not all (29, 30). Such inconsistency could be due in part to the large amounts of alcohol necessary to produce this defect; heavy drinking during pregnancy is uncommon, and the small numbers of exposed women in many studies have made it difficult to assess this association. Infant *ADH1C* genotype was associated with the risk of cleft lip and palate in our case-triad data and confirmed in a Danish data set (7). Furthermore, alcohol-metabolizing genes are expressed in placental tissue during the first trimester of pregnancy (12), when the critical stages of facial development occur.

Other *ADH* genes contribute to alcohol-metabolizing potential by functioning as homo- or heterodimers (3). Strong linkage disequilibrium across the *ADH* gene region makes it difficult to separate the effects of individual *ADH* genes. The highly active *ADH1B* variant was too uncommon (minor allele frequency in controls = 0.032) to examine its possible effect, along with maternal alcohol consumption, on oral cleft risk. However, excluding mothers and infants with this *ADH1B* variant moderately increased the risk estimate for clefts among persons in the intermediate-activity *ADH1C* group. This suggests a possible interplay among *ADH* genes, such that an increased metabolic rate in one may counteract the effect of slower metabolic rates in others.

While these findings are plausible, this study had some limitations. First, we cannot exclude the role of chance. The multiplicative interaction of alcohol effects across the high-activity and reduced-activity groups (Figure 3) did not reach statistical significance. Ideally we would like to replicate our findings in another population, but such a study would require DNA from case and control mothers and babies and information on maternal alcohol consumption in early pregnancy. French investigators who considered this question with a smaller study sample had participants with lower levels of drinking and little statistical power to detect genetic susceptibility to alcohol teratogenicity (31).

Recall bias is a potential concern. Mothers who gave birth to healthy infants may have been more or less likely to admit to drinking alcohol during pregnancy than mothers of infants with oral clefts; this would have biased the association. However, it is unlikely that such bias would vary by the genotype of the mother or the infant.

Another important source of uncertainty regarding these results is the stronger association between binge drinking and oral clefts in the intermediate-activity group than in the low-activity group—not the dose-response pattern that would be predicted (17). Given the imprecision of these estimates, the observed pattern may have been due to chance. It is also theoretically possible that a woman who drinks heavily and has slow alcohol metabolism (or whose fetus has slow alcohol metabolism) may be more likely to experience other alcohol-related problems such as infertility or fetal loss. Such women would not have entered our study, and their absence would have led to an underestimate of risk in this group. The role of *ADH1C* in modifying the association between maternal drinking and oral clefts was unclear when mothers' and children's genotypes were examined separately. Unless the mother's and child's genotypes are the same, classification by either mothers' or children's genotypes misclassifies some proportion of the other group, thus potentially clouding a genetic effect. The finding of genetic susceptibility in the combined analysis suggests the importance of both maternal and fetal genotypes when exploring genetic susceptibility in pregnancy-related outcomes.

Taking all these factors into consideration, the data provide coherent—but not conclusive—evidence that possession of the slow-metabolizing *ADH1C* variant by either the mother or the fetus increases the vulnerability of the fetus to alcohol-related oral clefts. This finding adds support to a causal interpretation of alcohol as a cause of oral clefts. Given that the majority of women and children of European descent carry at least 1 haplotype of the slow-metabolizing variant, these findings provide yet another reason for such women to be cautious in their alcohol consumption when considering pregnancy. Furthermore, data on maternal and fetal genetic susceptibility may help to identify other effects of drinking during pregnancy on a wider range of

fetal problems that have been suspected but not proven, including other birth defects and impairment of childhood neurodevelopment (32–36).

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Author affiliations: Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, North Carolina (Abee L. Boyles, Lisa A. DeRoo, Jack A. Taylor, Allen J. Wilcox); Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway (Rolv T. Lie); Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway (Astanand Jugessur); Craniofacial Research, Musculoskeletal Disorders, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia (Astanand Jugessur); and Departments of Pediatrics, Epidemiology, and Biological Sciences, College of Public Health, University of Iowa, Iowa City, Iowa (Jeffrey C. Murray).

Drs. Abee L. Boyles and Lisa A. DeRoo contributed equally to this work.

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